45. (Amended) The transgenic cell of claim 44, wherein said cell comprises two endogenous altered LXRα alleles that cannot express LXRα polypeptides that respond to dietary cholesterol.

REMARKS

I. Status of the Claims

Claims 1, 2, 4-14, 21, 23-27, 29, 44 and 45 are pending in the application. Claims 1, 2, 10-14, 21, 23-27, 29, 44 and 45 stand rejected under 35 U.S.C. §112, first paragraph for lack of enablement. Claims 1, 2, 4-14, 21, 23-27, 29, 44 and 45 are rejected under 35 U.S.C. §112, second paragraph for indefiniteness. The specific grounds for rejection, and applicants' response thereto, are set out in detail below.

II. Interview

Applicants and applicants' representative wish to thank Examiner Woitach for the courtesy of a telephonic interview held on June 18, 2003. Though no agreement was reached, it is believed that clarification of several issues during the teleconference will substantially advance the prosecution.

III. Rejection Under 35 U.S.C. §112, First Paragraph

Claims 1, 2, 4-14, 21, 23-27, 29, 44 and 45 are again rejected under the first paragraph of §112 on the grounds that the specification allegedly fails to provide "guidance" for the full scope of the claims. Applicants traverse.

To the extent that the examiner continues to have concerns over the enablement of heterozygotes, applicants point out that the specification (page 68, lines 20-24) clearly states that

heterozygotes display intermediate phenotypes – precisely what would be expected with the loss of one LXRα allele. This, in conjunction with the remainder of this response, is believed to obviate this aspect of the rejection.

The examiner also objects to the claims to the extent that they encompass mutations other than "disruptions," apparently meaning that alterations that do not truncate or delete portions of the LXRα sequence (*i.e.*, point mutations). The basis for this rejection is that (a) "the specific nature of the alteration" is not provided, and (b) the function of this molecule in cholesterol metabolism is complex. Applicants discussed this issue at length with the examiner during the interview, the substance of which is summarized and amplified below.

Applicants grant that the complexities of the LXRα molecule may not have been completely resolved at the time of filing. However, it is totally unnecessary, under the controlling legal precedent, for applicants to have a perfect understanding of how this receptor works. Moreover, it is not only unnecessary, but impractical, to provide a laundry list of alterations in the gene that result in loss of function. As the examiner is aware, making and testing mutations in a protein and the surrounding regulatory milieu is a trivial endeavor. Applicants have provided a critical insight into the role of LXRα, and it would take no more than routine experimentation to make and test mutations other than disruptions to find which have a "null" phenotype.

Moreover, in the action, it would appear that the examiner actually ***does*** believe that the claims are enabled: "Examiner would agree that various mutations or alterations of the LXRα coding sequence which result in a nonfunctional LXRα polypeptide wherein said animal lacks the capacity to respond to dietary cholesterol would be obvious and enabled over the specific example disclosed ... in the instant specification ...." Instead, it appears that the larger concern

is the "scope" of the animal being claimed, possibly encompassing mutations unrelated to LXRα.

Claim 1 is representative of the currently pending claims, and reads: "A transgenic mouse, the cells of which comprise at least one endogenous altered LXRα allele that cannot express LXRα polypeptide that responds to dietary cholesterol." This claim limits the subject matter of the invention to a transgenic mouse, cells of which have a mutated LXRα allele, and the mutant allele results (a) in reduced or no LXRα protein production, or (b) in the production of an LXRα protein that cannot respond to dietary cholesterol provided to the mouse. Thus, it is believed that there is a sufficient nexus between the mutated allele, the LXRα protein (or lack thereof) and the absence of a response to dietary cholesterol (*i.e.*, the "null" LXRα phenotype) to alleviate the examiner's concerns.

Another question raised in the action was whether the stated phenotype (lack of response to dietary cholesterol) is for the mouse, LXRα protein or the allele (see Office Action at page 7). Indeed, applicants have always intended that the phenotype is with respect to the protein, not the animal as a whole. Thus, another clarifying amendment is offered adding "polypeptide" to the term "LXRα." As such, it now should be clear to which element the phenotype attaches.

The next issue raised is that "response to dietary cholesterol" is a broad phenotype. However, the examiner again seems to be focusing on a "whole animal" phenotype, when this term is directed to the specific mutated LXRα polypeptide. Of course, dietary cholesterol implies feeding of the animal, but the dietary response limitation is directed to the LXRα ***polypeptide***. The claims have been clarified (see above) such that there is no question that the "response to dietary cholesterol" is directed to the polypeptide, and not the mouse.

Finally, the examiner suggests that the claims be amended to recite cholesterol accumulation and hepatomegaly. However, as discussed during the interview, the development of these conditions in the claimed mice ***is dependent upon provision of sufficient amounts dietary cholesterol***. Thus, the introduction of these terms is not appropriate since they depend upon factors outside the scope of the claimed mice, *i.e.*, the diet they may (or may not) be fed. Instead, applicants believe that the claims as amended, which define in absolute terms the inability of the mutated LXRα allele to produce an LXRα polypeptide that responds to exogenous cholesterol, appropriately define the subject matter invented by the applicants.

In light of the foregoing, applicants submit that the claims are fully enabled. Reconsideration and withdrawal of the rejection is, therefore, respectfully requested.

III. Rejections Under 35 U.S.C. §112, Second Paragraph

The examiner again rejects claims 1, 2, 4-14, 21, 23-27, 29, 44 and 45 as indefinite. Applicants traverse.

First, it is stated that it is unclear whether the term "that responds to dietary cholesterol" relates to the mouse as a whole, the LXRα allele or the protein. As discussed above, the claim has been amended to recite that the LXRα allele fails to produce a protein is that responds to dietary cholesterol. As such, it is believed that the claim is quite clear. Second, the examiner also questions "what specific response or what level of response is contemplated," and "what capacity is being measured." As discussed above, the response to dietary cholesterol refers to LXRα protein, not the mouse as a whole.

Third, as a final matter, the examiner argues that while the term "dietary cholesterol" is clear, the claims remain unclear in that a mouse provided a low diet of cholesterol (*i.e.*, 0.2%)

would not express "the phenotype." Once again, applicants point out that the claims to do not specify the phenotype of the mouse (*e.g.*, hepatomegaly). Rather, they specify and the phenotype of the ***protein***. With regard to the former, applicants agree that the phenotype of the mouse is variable, and depends on factors outside the scope of the claim -- that is precisely why applicants argue that hepatomegaly should not be included in the ***transgenic mouse*** claims. With regard to the latter, the phenotype of the protein – lack of ability to respond to exogenous (dietary) cholesterol – is absolute and independent of what amount of dietary is provided.

Thus, applicants respectfully submit that the pending claims are not indefinite, and are even more clear in their amended form as presented herein. Reconsideration and withdrawal of the rejection is, therefore, respectfully requested.

IV. Conclusion

In light of the foregoing, applicants respectfully submit that all claims are in condition for allowance, and an early indication to that effect is earnestly solicited. Should Examiner Woitach have any questions regarding this response, he is invited to contact the undersigned at the telephone number listed below.

Respectfully submitted,

Steven L. Highlander
Reg. No. 37,642
Attorney for Applicants

FULBRIGHT & JAWORSKI, L.L.P.
600 Congress Avenue, Suite 2400
Austin, TX 78701
512-536-3184

Date: June 19, 2003

APPENDIX A - MARKED UP COPY OF CLAIMS

1. (Twice amended) A transgenic mouse, the cells of which comprise at least one endogenous altered LXRα allele that cannot express LXRα polypeptide that responds to dietary cholesterol.

2. (Twice amended) The transgenic mouse of claim 1, wherein said cells comprise two endogenous altered LXRα alleles that cannot express LXRα polypeptides that [responds] respond to dietary cholesterol.

21. (Amended) A method for screening a candidate substance for the ability to reduce cholesterol levels in a mammal comprising:

(a) providing a transgenic mouse, the cells of which comprise at least one endogenous altered LXRα allele that cannot express LXRα polypeptide that responds to dietary cholesterol;
(b) treating said mouse with said candidate substance; and
(c) monitoring a cholesterol-related phenotype in said mouse,

wherein a reduction in said cholesterol-related phenotype in said mouse treated with said candidate substance, as compared to a similar mouse not treated with said candidate substance, indicates that said candidate substance reduces cholesterol levels.

26. (Amended) The method of claim 21, wherein said cells comprise two endogenous altered LXRα alleles that cannot express LXRα polypeptides that [responds] respond to dietary cholesterol.

27. (Amended) A method for screening a candidate substance for the ability to increase bile acid synthesis in a mammal comprising:

(a) providing a transgenic mouse, the cells of which comprise at least one endogenous altered LXRα allele that cannot express LXRα polypeptide that responds to dietary cholesterol;

(b) treating said mouse with said candidate substance; and

(c) monitoring a bile acid-related phenotype in said mouse,

wherein an increase in said bile acid-related phenotype in said mouse treated with said candidate substance, as compared to a similar mouse not treated with said candidate substance, indicates that said candidate substance increases bile acid synthesis.

44. (Amended) A transgenic mouse cell which comprises at least one endogenous altered LXRα allele that cannot express LXRα polypeptide that responds to dietary cholesterol.

45. (Amended) The transgenic cell of claim 44, wherein said cell comprises two endogenous altered LXRα alleles that cannot express LXRα polypeptides that [responds] respond to dietary cholesterol.